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Dominique Morlet[abc], Geneviève Demarquay[d], Frédérique Brudon[e], Catherine Fischer[abcf], Anne Caclin[abc]

[a] INSERM U1028, Lyon Neuroscience Research Center, Brain Dynamics and Cognition Team, Lyon, F-69000, France

[b] CNRS UMR5292, Lyon Neuroscience Research Center, Brain Dynamics and Cognition Team, Lyon, F-69000, France

[c] Université Lyon 1, Lyon, F-69000, France

[d] Hospices Civils de Lyon, Croix-Rousse Hospital, Neurology Department, Lyon, F-69000, France

[e] Tonkin Clinic, Villeurbanne, F-69100, France

[f] Hospices Civils de Lyon, Neurological Hospital, Functional Neurology and Epileptology Department, Lyon, F-69000, France

Corresponding author: Dominique Morlet
Lyon Neuroscience Research Center, Dycog team
69675 Bron Cedex, France
tel: + 33 (0)4 72 13 89 03
fax: + 33 (0)4 72 13 89 01
e-mail: dominique.morlet@inserm.fr

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MMN
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Highlights:

- The mismatch negativity (MMN) is normal in migraine patients.
- The N1 orienting component and the N2b are increased in migraine patients.
- Auditory processes up to attention triggering are preserved in migraine patients.
- Attention orienting to sound income and sound deviance are exacerbated in migraine.
- These observations suggest abnormal activation of attention-related frontal networks

Abstract

Objective

To investigate automatic event-related potentials (ERPs) to an auditory change in migraine patients.

Methods

Auditory ERPs were recorded in 22 female patients suffering from menstrually-related migraine and in 20 age-matched control subjects, in three sessions: in the middle of the menstrual cycle, before and during menses. In each session, 200 trains of tone-bursts each including two duration deviants were presented in a passive listening condition.

Results

In all sessions, duration deviance elicited a mismatch negativity (MMN) showing no difference between the two groups. However, migraine patients showed an increased N1 orienting component to all incoming stimuli and a prolonged N2b to deviance. They also presented a different modulation of P3a amplitude along the menstrual cycle, which tended to normalize during migraine attacks. None of the studied ERP components showed a default of habituation.

Conclusions

This passive paradigm highlighted increased automatic attention orienting to auditory changes but normal auditory sensory processing in migraineurs.

Significance

Our observations suggest normal auditory processing up to attention triggering but enhanced activation of attention-related frontal networks in migraineurs.

1. Introduction

Migraine is one of the most common headache disorders and affects 11% of the adult population (Stovner et al., 2007). Attacks are characterized by recurrent throbbing headaches accompanied by nausea, vomiting, photophobia, and/or phonophobia and are aggravated by movements (The International Classification of Headache Disorders, 2004). Between attacks, migraine patients may also show a hypersensitivity to visual, auditory, or olfactory stimuli (Main et al., 1997; 2000). Moreover, sound/light-induced headaches are frequent in migraine patients (Vingen et al., 1999; 2004). The pathophysiological basis of such hypersensitivity to external stimuli is currently not completely elucidated.

In line with these symptoms, electrophysiological studies have revealed changes in cortical excitability between migraine attacks. Increased attention orienting to new incoming stimuli had been long ago demonstrated in migraine patients. The initial (or early) Contingent Negative Variation (iCNV), which reflects the orienting properties of a warning stimulus in an active paradigm, has been found to be increased in migraine (Maertens de Noordhout et al., 1986), preferentially just before an attack (Kropp and Gerber, 1998), but not systematically (Böcker et al., 1990; Mulder et al., 2001). A default in the habituation of several event-related potentials (ERPs) to visual and auditory stimuli has also been observed in migraine patients in numerous studies (for a review, see Coppola et al., 2009), although not systematically (Oelkers et al., 1999; Sand and Vanagaite Vingen, 2000; Omland et al., 2013). Using an auditory habituation paradigm made of small consecutive trains of tones (Woods and Elmasian, 1986), we also found normal habituation pattern of the sensory N1 in migraineurs (Demarquay et al., 2011). Interestingly, this passive paradigm allowed to investigate the automatic response to the first stimuli of stimulation trains, and revealed that migraine patients exhibited a drastically augmented N1 orienting component, a fronto-central negative component appearing after the obligatory sensory N1 when the inter-stimulus interval is greater than 4 s (Näätänen and Picton, 1987; Alcaini et al., 1994). The response to standard stimuli inside the trains also exhibited enhanced negative potentials in the descending slope of the N1 wave. By comparison with the augmented N1

orienting component observed in response to the first stimuli of the trains, we called this additional component "residual orienting component" and we concluded that migraine patients showed exacerbated attention orienting not only to first stimuli after a silent gap but also to repeated similar incoming stimuli.

The electrophysiological studies described above showed abnormal responses not only to attended warning stimuli but also to passively endured stimuli. They emphasized attention-orienting exacerbation and/or habituation deficit in migraine without clearly disentangling basic auditory processing dysfunction and abnormal orienting processes. The use of passive oddball paradigms is of particular interest here because it allows studying both automatic sensory responses to auditory changes and automatic attention triggering. Indeed, in those paradigms, a rare and random change in repetitive stimulation elicits a negative response (Mismatch Negativity or MMN) disclosed when the response to the standard is subtracted from the response to the deviant. MMN is attributed to discriminative processes using memory traces developed from the previous stimulation (review in Näätänen et al., 2001; Näätänen et al., 2007; Näätänen et al., 2011). It is noteworthy that the memory traces probed by the MMN are thought to reflect the outcome of perceptual processing (Näätänen and Winkler, 1999; Näätänen et al., 2011) and further that MMN occurs automatically, even if subject's attention is not directed to the sounds (Näätänen et al., 1993). Nevertheless, if deviant stimuli are salient enough, attention-orienting processes can be triggered, and an N2b-P3a complex (brain orienting response) is further obtained following the MMN (Näätänen et al., 1982). In contrast, presenting a second consecutive deviant drastically diminishes the MMN (and subsequent orienting responses), which has been called "short-term habituation of the MMN" (Sams et al., 1984). This phenomenon was explained by the simultaneous occurrence, for the repeated deviant, of mismatch processes with the (declining) neuronal model of the standard and match processes with the neuronal model of the deviant. Altogether, the study of ERPs triggered by a rare change in auditory stimulation thus offers the advantage to assess, in a passive listening situation, the integrity of pre-attentive stages of perceptual processing, as indexed by the MMN, as well as the automatic triggering of attention, indexed by the N2b-P3a complex. For these reasons, passive auditory oddball paradigms have been used in a very large number of ERP studies in various pathologies (review in Näätänen, 2003;

Naatanen et al., 2012), but surprisingly very rarely in migraine.

Indeed, most of the oddball paradigm studies in migraine have required an active detection of deviant tones and they mainly focused on the P300 in response to targets, which was found to be altered in migraine patients (Drake et al., 1989; Mazzotta et al., 1995; Wang et al., 1995). The investigation of brain mechanisms to a stimulus change during passive listening has been rarely reported in migraine patients. Only one study investigated the MMN in adult migraineurs and reported increased N1 and MMN latencies, suggesting a hypo-activity of automatic cortical processes (de Tommaso et al., 2004). Two recent paediatric migraine studies also pointed to subtle MMN alterations in these patients (Valeriani et al., 2009; Korostenskaja et al., 2011). One study (Wang and Schoenen, 1998) explored the amplitude of an N2-P3a complex in response to deviant stimuli and reported for migraine patients a potentiation of this response in successive blocks, contrasting with a habituation in controls.

The aim of the present study was thus to investigate the specific response to deviant stimuli in migraine patients, from the pre-attentive processes (MMN) to the attention-orienting processes (N2b, P3a), and to assess the habituation of the different components. Abnormalities of the MMN would suggest dysfunction in basic auditory processing of migraine patients. In light of our previous results, we expected a pathological brain orienting response to deviants.

2. Methods

The present analysis is the second part of a larger auditory ERP study conducted in migraineurs using small trains of repeated standard tones with occasional deviant stimuli. The first part of the analysis focused on the responses to standards and their habituation patterns (Demarquay et al., 2011). Here we explore the response to deviant stimuli.

2.1 Migraine patients and healthy subjects

Twenty-two female migraine patients suffering from menstrually-related migraine without aura (A1.1.2 in ICHD 2004) were included in the study (mean age ± SD: 27 years ± 7; disease duration: 12 years ± 8; attack frequency: 2 ± 1 per month). Migraine patients and controls were recruited through advertising in Lyon University and INSERM administration. A neurologist (CF, FB or GD) subsequently examined eligible subjects.

Twenty age-matched female controls participated in the study (28 years ± 9). Exclusion criteria for all subjects included chronic daily headache, known morphological brain abnormality, current substance abuse, and migraine preventive medication. 14 migraine patients and 11 controls took oral contraceptives ($\chi^2 = 0.0649$, $p = 0.799$).

All subjects gave their written informed consent (CCPPRB centre Léon-Bérard, Lyon, A 06-107, 04/20/06) and were remunerated for their contribution.

2.2 Recording procedure

The recording procedure has been described in detail previously (Demarquay et al., 2011).

Patients and healthy subjects were recorded in 3 different sessions, in the middle of the menstrual cycle (session 0, S0, day 15 ± 4 of the on-going cycle), before menses (session 1, S1, day -1 ± 1 of the cycle), and at the beginning of the menses (session 2, S2, day 1 ± 1 of the cycle). As a general rule, S2 immediately followed S1 (mean delay = 2 days ± 1), except for 1 healthy subject and for 3 patients,

for whom S1 and S2 were in separate cycles. Session 0 randomly preceded or followed S1 and S2. S0 was before S1 in 12/22 patients and in 13/20 healthy subjects ($\chi^2 = 0.923$, $p = 0.337$).

Among the 22 migraineurs, ERPs were recorded during a migraine attack in 12 patients (session 1 for 5 patients; session 2 for 6 patients; session 0 for 1 patient). In all patients, the attack occurred before the onset of the ERP recording and lasted until the end; medication was given at the end of recording session.

During the recording sessions, the subject sat in a comfortable armchair in a quiet room. She was instructed to watch a silent movie of her choice and not to pay attention to the auditory stimuli.

EEG was recorded continuously from 7 scalp electrodes placed at frontal (Fz, F3, F4), central (Cz), and parietal (Pz) sites, and at the two mastoids (M1, M2). The reference electrode was placed on the tip of the nose, the ground electrode on the forehead. One bipolar EOG derivation was recorded from 2 electrodes placed on the supra-orbital and infra-orbital ridges of the right eye. Using a Micromed System98 EEG recording system, the signal was amplified (band-pass 0.3-100 Hz), digitized (sampling frequency 1024 Hz) and stored for off-line analysis. One stimulation session lasted about 45 minutes without any interruption.

2.3 Auditory paradigm

The stimuli were delivered binaurally through insert earphones at an intensity of 65 dB HL.

In each recording session, 200 trains of auditory stimuli were presented with an average of 10 stimuli per train (random number from 8 to 12). The inter-train interval ranged between 5.5 and 8.0 seconds (mean value 6.75 s). Within trains, stimulus onset asynchrony was 610 ms.

The stimuli were spectrally rich tone bursts (fundamental frequency 800 Hz). The more frequent stimuli (standards) had a duration of 75 ms, including 5-ms rise and fall times. Duration deviants (duration 30 ms) were used, because duration changes (with deviants shorter than standards) are known to provide robust and reproducible MMNs (Tervaniemi et al., 1999). Two deviant tones were pseudo-randomly included in each train. The first deviant was randomly presented after 3 to 9 consecutive standards. In each recording session, one hundred trains (50% of the trains) obeyed the rule routinely used in oddball paradigms, namely at least 2 standards were presented between the first

and the second deviant. In the other half of the trains, the second deviant appeared immediately after the first one (repeated deviant). One recording session thus included 300 "generic" deviants appearing after at least 2 standards (200 generic deviants being first deviants and 100 generic deviants being second deviants) and 100 "repeated deviants" appearing immediately after another deviant. Figure 1 illustrates the design and the timing of auditory stimulation.

Additionally, 20% of the trains ended with a salient stimulus (environmental sound). Evoked responses for these novel stimuli are beyond the scope of the present report.

2.4 Event-related potentials

The software package for electrophysiological analysis (ELAN) developed at the Lyon Neuroscience Research Center (Aguera et al., 2011) was used for ERP analysis. Responses to standards and to deviants were considered for averaging for an epoch of 700 ms including a pre-stimulus period of 100 ms. Epochs showing peak-to-peak deflections larger than ± 100μV were rejected. One patient showed a large stimulation artifact at the mastoids 15 ms after stimulus onset in the 3 recording sessions. For this patient, an independent component analysis (ICA) was used in order to isolate and remove this unwanted component.

The ERPs were baseline-corrected by subtracting the mean value of the signal during the 100 ms prior to the stimulus. A 30-Hz low-pass digital filter (bidirectional Butterworth, 6^{th} order) and a 2-Hz high-pass filter (bidirectional Butterworth, 2^{nd} order) were applied to the averaged epochs.

To fulfill the different aims of the study, we performed the following types of averages in each session for each participant: 1) averages of "generic standards" (in black Figure 1), from which the first 3 standards in the trains and the standards that immediately followed a deviant were excluded; 2) averages of "generic deviants" (in black Figure 1), from which the deviants that immediately followed another deviant were excluded; 3) averages of "first" deviants, which included only the first deviant in each train; 4) averages of "repeated deviants" (in grey Figure 1), which included only the second deviants that immediately followed a first deviant. To assess long-term habituation averages 1 and 2 were performed separately in the first half (first 100 trains) and in the second half (last 100 trains) of

each session. Averages 3 and 4 were used to investigate the so-called "short-term habituation" to deviance.

2.5 Statistical analysis

In a first stage, we studied the response to generic deviants and to generic standards. In a second stage, the response to generic standards was subtracted from the response to generic deviants in order to classically assess the response specific to deviance. A mismatch negativity (MMN) was expected around 100-150 ms after the point in time when the deviant stimulus turns out to be shorter than standards (in our paradigm, 25 ms after stimulus onset). Based on previous studies using similar paradigms (Jung et al., 2006; Ruby et al., 2008), we also expected a central negative N2b and a positive P3a following the MMN. At both stages, analyses were performed along two streams. Firstly, we assessed ERP amplitudes around the maxima of the expected components (N1 for the standard and deviant ERPs; MMN, N2b, and P3a for the subtraction ERP). The time-windows and electrode sites of interest for the assessment of the expected components were derived from the observation of the grand averages over sessions and subjects. Secondly, in order to uncover possible abnormalities in the ERPs of migraine patients away from the peaks of the main expected components, we also performed a direct comparison of the ERPs of migraine patients and healthy subjects using Kruskal-Wallis tests at each time sample (between 0 and 300 ms) and each electrode. For this analysis the data were pooled over the three sessions (see also Demarquay et al., 2011). To correct for multiple comparisons, we only considered as significant the effects lasting more than 15 ms (Guthrie and Buchwald, 1991). This procedure allowed defining two other time windows of interest (one in the descending slope of N1 and one in the descending slope of N2b), where we further assessed session and habituation effects. The two streams of analysis provide objective measures of the different ERP components, as they do not depend of visual selection of individual peaks.

In all cases, ANOVAs were applied to ERP mean amplitudes in the time-windows of interest to investigate the effects of the between-subject factor Pathology (2 levels, 20 healthy subjects versus 22 migraine patients) and the within-subject factors Session (3 levels, S0 = middle of the menstrual cycle,

S1 = before menses, and S2 = during menses) and Long-Term Habituation (LTH, 2 levels, first half and second half of the recording sessions). When analyzing the N1, the within-subject factor Type of stimulus (2 levels, generic standard versus generic deviant) was also considered. The so-called "short-term habituation" to deviance was separately investigated in an ANOVA with Pathology and Session factors, comparing the response to the first deviant and the response to the immediately following deviant (within-subject factor Short-Term Habituation, STH, 2 levels, first deviant versus repeated deviant).

A saturated ANOVA model was used to test for all possible factor interactions. When appropriate, Greenhouse-Geisser (G-G) correction of the degrees of freedom was applied. For post-hoc comparisons we used Tukey's HSD test. Statistical analyses were performed with the Statistica software (StatSoft Inc).

3. Results

Across the three recording sessions, the mean number of accepted generic deviant trials was 266 ± 32 for the migraine patients and 268 ± 27 for the healthy subjects (i.e. 11% of rejected deviant trials on average).

3.1 N1 sensory and orienting components to generic standards and deviants

In both populations, N1 peaked around 85 ms (Figure 2a) and displayed a central topography with the typical polarity inversion at the mastoids of the sensory N1 component (Figure 2c). The sensory N1 component was assessed in the 75-95 ms time-window at electrode Cz. Sample-by-sample Kruskal-Wallis tests comparing the responses to standard stimuli of patients and controls showed significant differences in the 100-120 ms time-window at F3, Fz, F4, and Cz (see Figure 3). Similar differences were obtained in this latency range for the deviant ERPs. This time-window corresponds to the residual orienting component of the N1, hidden in the descending slope of the sensory N1 and previously found enhanced in migraine patients in response to standard stimuli (Demarquay et al., 2011). We assessed the amplitude of the N1 orienting component as the mean potential in the 100 - 120 ms time-window on a cluster including the 4 frontal-central electrodes.

The results of four-way ANOVAs on the measures of N1 sub-components, with Pathology as between-subject factor and with Session, Type of stimulus, and Long-Term Habituation as within-subject factors are displayed in Table 1. Both sub-components showed a significant long-term habituation that did not interact with Pathology. The type of stimulus influenced the two components with opposite effects: deviants triggered a larger N1 orienting component than standards, but a smaller N1 sensory component. For the sensory N1, the effect of the type of stimulus can be attributed to the acoustical difference between the two sounds: the less energetic shorter deviant gives rise to smaller obligatory ERP components, as we already observed in a number of other studies using the same MMN paradigm (Fischer et al., 1999; Ruby et al., 2008). In the N1 orienting component time-window,

the effect of the type of stimulus can be attributed to an overlap with the onset of the MMN: the response to deviants shows enhanced negative potentials at frontal sites starting from 200 ms, i.e. in the descending slope of N1. As expected from the Kruskal-Wallis tests, a significant effect of Pathology was found for the N1 orienting component. Migraine patients thus present an enhancement of negative potentials at the latency of the orienting component in the late part of the N1, as already observed for standard stimuli (Demarquay et al., 2011). The present study suggests that this enhancement does not differ between deviant and standard stimuli (see Figure 3, c and d).

3.2 Main components of the deviance-specific response: MMN, N2b, P3a

A negative difference wave was observed in both populations after 100 ms in the specific response to deviance (Figure 2b). Visual inspection of the difference wave and its topography (Figure 2, b and c) made it possible to disentangle an MMN, maximal at frontal sites and characterized by a pronounced polarity inversion at both mastoids around 135 ms, followed in both populations by a central negativity without any accompanying polarity inversion (N2b) peaking around 165 ms and a central positivity (P3a) peaking around 250 ms. We assessed MMN amplitude as the mean potential between 115 and 145 ms measured at the 3 frontal electrodes (F3, Fz, and F4). N2b and P3a amplitudes were measured at Cz. N2b amplitude was measured as the mean potential between 145 and 200 ms. The junction between N2b and P3a (i.e. the point where the response changes its polarity between the two components) occurs around 200 ms and seems different in the two groups. For P3a we thus assessed the mean of positive potentials between 200 and 300 ms, in order to avoid contaminating the estimate with the latest part of the N2b. Figure 4 displays the measures of MMN (Fig. 4a), N2b (Fig. 4b), and P3a (Fig. 4c) amplitudes for each group and in each recording session.

3.2.1 Long-term habituation of the components of the deviance-specific response

Figure 5 illustrates the effects of long-term habituation on the difference response in the three recording sessions at frontal sites (average of F3, Fz, and F4) where MMN is measured and at Cz where N2b and P3a are measured. The results of three-way ANOVAs performed on the measures of

the three components, with Pathology as between-subject factor and Session and LTH as within-subject factors are shown in Table 2. None of the three components showed a significant effect of Pathology. Long-term habituation significantly affected N2b and P3a and showed no significant interaction with Pathology. MMN did not habituate over the course of an entire session, in accordance with previous unpublished data from our lab using a similar protocol.

For N2b, an effect of Session was observed, with larger N2b in the pre-menstrual session (post-hoc S1 versus S2 $p = 0.04$, S1 versus S0 $p = 0.10$, Fig. 4b). This N2b amplitude variation as a function of the recording session combined with the LTH of this component resulted in an interaction between Session and LTH. However, the effect of the menstrual cycle on N2b amplitude was not different between patients and healthy subjects.

For P3a, an interaction between Pathology and Session was the result of a smaller P3a in the menstrual session than in the session in the middle of the menstrual cycle for control subjects only (post-hoc S2 versus S0 $p = 0.04$ for healthy subjects, $p = 0.41$ for patients, Fig 4c). Thus, in the menstrual session, i.e. in the session where migraine attacks preferentially occur, the migraine patients did not show the decrease in P3a component observed in healthy subjects. In order to highlight a possible effect of a migraine attack on P3a, we performed an additional analysis differentiating the 11 patients who actually presented a migraine attack during one of the recording sessions (S1 or S2) and the 10 patients who did not, excluding the only subject who experienced headache during the session in the middle of the cycle (S0). A 3-way ANOVA was applied to P3a amplitude, with the between subjects factor “migraine-attack” (3 levels: control subjects, patients with and patients without migraine attack) and LTH and Session as within-subject factors. In this analysis, the Session factor had only 2 levels, the between menses session (S0) and a peri-menses session, possibly with a migraine attack. For patients with a migraine attack, the peri-menses session was S1 for 5 patients and S2 for 6 patients. For the patients who did not report a migraine attack and for the controls, the peri-menses session was randomly chosen to be S1 (5 patients and 9 controls) or S2 (5 patients and 11 controls, see (Demarquay et al., 2011), for a similar analysis). This additional ANOVA resulted in a significant interaction between the intra-subject factor “Session” and the between-subject factor “migraine attack”

(F(2,38) = 4.653, p = 0.016). Post-hoc tests were not significant. However, as displayed in Figure 4d, patients with a migraine attack showed a tendency for a decrease in P3a amplitude in the peri-menses session like the healthy subjects, while patients without a migraine attack showed a tendency for an increase in P3a amplitude in the peri-menses session. Another 3-way ANOVA using LTH and Session as within-subject factors, but restricted to the migraine patients (2 levels: patients with and without migraine attack), confirmed this different modulation of P3a amplitude by migraine attacks, with a marginally significant interaction between the intra-subject factor "Session" and the between-subject factor "migraine attack" (F(1,19) = 4.300, p = 0.052).

3.2.2 "Short-term habituation" of the components of the deviance-specific response

Figure 6 shows the difference responses restricted to the first deviants in the trains (first deviant minus generic standard) and to the deviants that immediately followed the first deviants (repeated deviant minus generic standard), grand averaged over the 3 sessions. It illustrates the effects of the so-called "short-term habituation" on the components of the response to deviance. Table 3 displays the results of ANOVAs performed on MMN, N2b, and P3a components with Pathology as between-subject factor and with Session and STH as within-subject factors. There was a significant effect of STH on the three components (MMN, N2b, P3a), the response globally collapsing to repeated deviance in both populations. For N2b, there was an interaction between STH and Pathology due to a non-significant tendency (p = 0.26) for this component to be larger in migraine patients than in controls in response to the first deviant. For P3a an interaction between STH, Pathology and Session resulted from smaller amplitude of the P3a to the first deviant in S2 than in S0 for the healthy subjects (post-hoc S2 versus S0 p = 0.07 for healthy subjects), as also observed above for generic deviants.

3.3 Direct comparison of responses to deviance in migraine patients and in healthy subjects: "Late N2b"

To investigate effects of pathology in the specific response to deviance outside the maxima of the expected components, we considered the sample-by-sample difference between the difference responses (generic deviants minus generic standards) of Patients and Controls averaged over the three

sessions. This was done separately for the first half (first 100 trains) and the second half (last 100 trains) of the recordings because of the large LTH of the N2b and P3a components (see above). We ran sample-by-sample Kruskal-Wallis tests at each electrode and each time sample between 0 and 300 ms post-stimulus to compare the two groups. A significant difference between the two groups was observed at the 3 frontal electrodes in the 190 – 210 ms time-window in the first half of the sessions (Figure 7). Indeed, the "Patients minus Controls" difference curve showed a maximum around 200 ms at frontal sites, with the N2b thus appearing to last longer in migraine patients than in controls. To further investigate the effects of Session on this "Late N2b" which was different between groups, we performed a two-way ANOVA on the mean potentials measured between 190 and 210 ms for the first 100 trains of each session on a cluster including the 3 frontal electrodes with Pathology as between-subject factor and Session as within-subject factor (see the measures in Figure 7d). This "late N2b" was significantly enhanced in migraine patients ($F(1,40) = 5.106$, $p = 0.029$), which was expected based on the Kruskal-Wallis tests reported above. There was also a global effect of Session ($F(2,80) = 3.630$, $\varepsilon = 0.926$, $p = 0.035$), with a collapse in the menstrual session (S2 versus S1 $p = 0.04$ and S2 versus S0 $p = 0.06$), but without any interaction with Pathology ($F(2,80) = 1.470$, $p = 0.237$). In other words, migraine patients show enhanced negative frontal potentials in the late part of N2b, mostly evident in the first half of the sessions, when N2b and P3a have not yet habituated.

4. Discussion

Sensory processing has been extensively studied in migraine patients using ERPs (Schoenen et al., 2003), and has mostly concerned habituation to repeated sensory stimulation in passive paradigms, as well as brain responses to sensory changes in active paradigms. However, the specific response to unexpected change in auditory stimulation during passive listening was scarcely reported. In this study, we investigated the brain processes triggered by shorter tones randomly presented among repeated tones in migraine patients in a situation of passive listening during three sessions along the migraine cycle. The paradigm made it possible to study the MMN reflecting automatic mismatch detection and subsequent N2b and P3a components reflecting attention orienting (Näätänen and Gaillard, 1983). MMN was normal in migraine patients. However, along all recording sessions, migraine disease modulated the responses at three stages of processing where attention-orienting processes are thought to occur. First, around the descending slope of the N1, at the latency of a possible residual orienting component (around 105 ms), fronto-central negative potentials were enhanced in migraine patients, both for standard and for deviant tones. Second, in the differential response to deviance (deviants minus standards), frontal potentials were negatively enhanced in migraine patients during the descending slope from the N2b to the P3a (around 200 ms). Finally, P3a amplitude was modulated differently along the menstrual cycle in the two groups, and tended to normalize during migraine attacks.

4.1 Normal automatic mismatch detection in migraine

In the control group, randomly presented short-duration deviant tones elicited an MMN, followed by N2b and P3a components. MMN is considered to be elicited pre-attentively (review in Näätänen and Winkler, 1999), and to reflect automatic mismatch processes between the incoming deviant and a memory trace of the previous repeated standard. As expected, immediately repeating the deviant tone drastically diminished the amplitude of the MMN and of subsequent components (so-called “short-

term habituation" of the MMN in Sams et al., 1984). In contrast, MMN amplitude did not evolve over the course of the entire recording sessions (i.e., did not show any significant long-term habituation), contrarily to subsequent attention-triggering mechanisms (N2b - P3a), in accordance with previous observations (Lyytinen et al. (1992), and own unpublished observation over blocks of 3 hours of stimulation).

Statistical analysis did not reveal any difference in MMNs between migraineurs and controls, suggesting that up to the level of auditory processing where MMN operates, this processing does not show any impairment in migraine. The current results extend our previous findings of preserved sensory N1 component in migraine (Demarquay et al., 2011) by showing that the sensory memory traces underlying MMN generation are also preserved in migraine. Our results contrast with a report suggesting that MMN habituates in controls but not in migraineurs (de Tommaso et al., 2004). In this earlier report, the stimulation paradigm was similar to our paradigm. However, MMN was measured in the deviant ERP rather than in the usual deviant minus standard ERP. Considering this important methodological discrepancy with our study and the fact that MMN latencies reported in de Tommaso et al. (2004) were globally late in controls and in patients (around 200 ms), we can speculate that these MMN measures rather concerned the N2b. Similarly, in their pediatric MMN study, Valeriani et al. (2009) reported an habituation deficit of the MMN in migraine, but did not attempt to disentangle MMN from N2b. In an attempt to dissociate the sensory mismatch processes from the subsequent attention alerting processes, we assessed separately the mean amplitudes of the potentials at the respective latencies of MMN and N2b. Other techniques such as trial-by-trial time-frequency analysis of the EEG, beyond the scope of the present report, could be helpful to definitely exclude differences in change detection processes between migraine patients and controls.

Neither the present study, nor our previous migraine study (Demarquay et al., 2011) of auditory ERPs in a passive listening situation evidenced any abnormality in basic sensory processing, including MMN generation. These observations are consistent with previous studies showing no significant difference between migraineurs and controls with regard to sensory N1 and P2 component (Drake et al., 1989; Sand and Vanagaite Vingen, 2000).

4.2. Abnormal attention orienting in migraine

Contrasting with the fairly normal MMN observed in migraine patients, we observed at two different processing stages enhanced frontal negative potentials in migraine patients, which suggest an increased attention orienting (Halgren et al., 2011). Patients showed larger negative frontal potentials firstly in the descending slope of the N1 for responses to both standard and deviant tones, and secondly in the late part of the N2b in the response specific to deviance (deviants minus standards difference wave).

In a previous report (Demarquay et al., 2011), we already reported such increased fronto-central negative potentials for standard tones in migraine. This effect was peculiarly pronounced when tones appeared at the beginning of the trains of stimuli (i.e. after a long silence), when the orienting component (or component III, Näätänen and Picton, 1987) of the N1 is large (Alcaini et al., 1994). We interpreted these enhanced fronto-central negative potentials in response to any standard tone as a residual N1 orienting component. Here we show that a comparable effect is obtained with deviant tones, suggesting that augmented orienting processes might actually be elicited by any incoming auditory stimulus in migraine. Interestingly, the increase of the N1 orienting component observed in migraine patients occurs earlier than the MMN (see Figure 2). As MMN appears fairly normal in migraine, it can be hypothesized that these abnormal early orienting processes do not interfere with the sensory memory and comparison processes underlying MMN generation.

Migraine patients also showed augmented frontal negative potentials in the deviance-specific response located in the descending slope of N2b. This effect was mostly evident in the first half of all sessions. N2b is a fronto-central subcomponent, which typically arises in active paradigms and has been associated with attention-triggering (Snyder and Hillyard, 1976; Näätänen and Gaillard, 1983; Kiehl et al., 2001) and cognitive control encompassing response inhibition to a non-target deviant, response conflict, and error monitoring (Folstein and Van Petten, 2008; Schwartze et al., 2011). N2b was shown to be associated with higher order processing than the MMN (Ritter et al., 1992). However N2b can also occur in passive oddball paradigms, in particular when the difference between standards and deviants is large enough (Näätänen et al. (1982); see also Ruby et al. (2008) for an example of N2b

recorded in a passive oddball paradigm using duration deviants). Although participants in our study were instructed to watch a silent movie and to ignore auditory stimuli, their attention might have been involuntarily oriented to the deviant stimuli and the prolonged negative potentials at the end of N2b observed in migraineurs could reflect an abnormal activity at the moment of this involuntary shift of attention.

Moreover, P3a amplitude was modulated along the menstrual cycle in both groups. Controls showed a smaller P3a during menses than in the session between menses. As far as we know, this was never described in the literature. The overall migraine population showed an opposite pattern, with an enhanced P3a in the menstrual session. This abnormality tended to normalize during migraine attacks. In a previous study (Demarquay et al., 2011), we already observed P3a abnormalities depending on the recording session. However, whereas the present result concerned the P3a individualized in the response specific to deviance, the former result concerned the P3a in response to the first tones of the trains, a component partially overlapping the sensory P2. Thus, the two results can hardly be compared. Nevertheless, both results have in common a normalization of P3a amplitudes during migraine attacks, in accordance with previous observations concerning several other components (Kropp and Gerber, 1995; Kropp and Gerber, 1998; Evers et al., 1999; Judit et al., 2000).

As a whole, our results reveal ERP abnormalities arising in migraine patients at stages of processing where attention-orienting mechanisms are susceptible to operate. They are in keeping with findings using active paradigms (and thus involving attention), showing abnormal cognitive responses like the P300 to targets (Drake et al., 1989; Wang et al., 1996; Evers et al., 1998) or the CNV to warning stimuli (Maertens de Noordhout et al., 1986; Kropp and Gerber, 1993). As the main generators of N1 orienting component, N2b and P3a are thought to be located in frontal areas (see Alcaini et al. (1994) for the N1 orienting component, Halgren et al. (2011) for the N2b and Polich and Criado (2006) for P3a), the abnormal automatic attention orienting towards acoustic stimuli observed in migraineurs may reflect abnormal attention-related frontal networks in migraine.

4.3. Sensory processing and attention orienting in migraine

To sum up, the present ERP findings allow setting the working hypothesis of normal sensory stages of auditory processing in migraine, but exacerbated mechanisms of automatic attention orienting to the auditory stimulation, possibly relying on an abnormal involvement of frontal networks. As emphasized above, our results are in line with previous studies that showed normal N1 and P2 sensory responses but altered cognitive responses like the iCNV, and P300. The apparent discrepancy with previous reports of a lack of habituation of auditory ERPs in migraine (Wang et al., 1996; Ambrosini et al., 2003) could be related to the paradigms used in these studies. Indeed, lack of habituation was observed in paradigms using intensity dependence of auditory potentials (IDAP), where sound intensity varies randomly within blocks. No habituation deficit was observed when stimulus intensity changes did not occur within blocks (Sand and Vanagaite Vingen, 2000), or in paradigms not involving intensity variations such as ours (Demarquay et al., 2011). We can speculate that random changes in the auditory stimulation might be more arousing than unvarying stimuli, and thus more likely to automatically engage attentional networks. This is in keeping with the present findings of an increased attention orienting to rare changes occurring in streams of otherwise repetitive tones. Furthermore, a link between habituation deficits in migraine and abnormal orienting activity has been already proposed by Siniatchkin et al. (Siniatchkin et al., 2000).

In the visual modality, the habituation of ERPs has been widely tested in migraine patients, mainly using pattern-reversal stimuli, with contrasting results (Schoenen et al., 1995; Afra et al., 1998; Wang et al., 1999). One study suggested that the visual habituation deficit in migraine depends on the stimulus characteristics (Oelkers et al., 1999), but a recent one using individual identification of visual evoked peaks in a blinded evaluation design found normal habituation in interictal migraineurs, with similar check-size effects in patients and controls (Omland et al., 2013). Besides, recent studies showed an increased automatic attentional response to sudden-onset visual events in migraineurs (Mickleborough et al., 2011a). Interestingly, in line with our observation of an enhancement of the N1 orienting component in auditory ERPs, these authors showed an early attention effect in the visual N1 ERP component in migraine patients (Mickleborough et al., 2011b). Thus, in the visual modality also,

further studies might possibly enlighten a link between observed habituation deficits and attention orienting exacerbation.

4.4. Methodological issues

In the present study, in an attempt to follow a migraine cycle, we only recorded patients with menstrually-related migraine. This strategy indeed allowed us to record 11 patients during a migraine attack. However, as patients were not requested to fulfill migraine diaries, it might be possible that, during some recordings, some patients were in a preictal state, a state where cortical excitability has been shown to fluctuate. This would be more likely for sessions S1 and S2, i.e., the sessions around menses. Indeed, before an attack, migraineurs show a normalization of the interictal lack of habituation of CNV (Kropp and Gerber, 1995; Kropp and Gerber, 1998; Siniatchkin et al., 1999) and of IDAP potentials (Judit et al., 2000). It is however noteworthy that, except for the P3a, the between-group differences observed in the present study (enhanced N1 orienting component and enhanced late N2b in migraine patients) did not depend on the recording sessions, suggesting that these effects are not modulated along the migraine cycle. We cannot exclude that a precise sorting of the recording sessions in "interictal" "pre-ictal" and "ictal" could allow to reveal further differences between migraine patients and controls.

In conclusion, our study shows normal auditory sensory processing in migraine patients but increased automatic attention orienting processes to auditory changes (and more generally to any incoming auditory stimulus). The pathophysiologic basis of such heightened attentional response recorded in migraineurs is still unknown, but could, at least partially, be linked to the close relationship observed between environmental stimuli and migraine. Understanding the links between photo/phonophobia and an increased automatic attention orienting in migraine is a challenge for future studies.

References

Afra J, Cecchini AP, De Pasqua V, Albert A, Schoenen J. Visual evoked potentials during long periods of pattern-reversal stimulation in migraine. Brain 1998; 121: 233-241.

Aguera PE, Jerbi K, Caclin A, Bertrand O. ELAN: a software package for analysis and visualization of MEG, EEG, and LFP signals. Comput Intell Neurosci 2011; 2011: 158970.

Alcaini M, Giard MH, Thevenet M, Pernier J. Two separate frontal components in the N1 wave of the human auditory cortex. Psychophysiology 1994; 31: 611-615.

Ambrosini A, Rossi P, De Pasqua V, Pierelli F, Schoenen J. Lack of habituation causes high intensity dependence of auditory evoked cortical potentials in migraine. Brain 2003; 126: 2009-2015.

Böcker KB, Timsit-Berthier M, Schoenen J, Brunia CH. Contingent Negative Variation in migraine. Headache 1990; 30: 604-609.

Coppola G, Pierelli F, Schoenen J. Habituation and migraine. Neurobiol Learn Mem 2009; 92: 249-259.

de Tommaso M, Guido M, Libro G, Losito L, Difruscolo O, Sardaro M, et al. Interictal lack of habituation of mismatch negativity in migraine. Cephalalgia 2004; 24: 663-668.

Demarquay G, Caclin A, Brudon F, Fischer C, Morlet D. Exacerbated attention orienting to auditory stimulation in migraine patients. Clin Neurophysiol 2011; 122: 1755-1763.

Drake ME, Jr., Pakalnis A, Padamadan H. Long-latency auditory event related potentials in migraine. Headache 1989; 29: 239-241.

Evers S, Bauer B, Grotemeyer KH, Kurlemann G, Husstedt IW. Event-related potentials (P300) in primary headache in childhood and adolescence. J Child Neurol 1998; 13: 322-326.

Evers S, Quibeldey F, Grotemeyer KH, Suhr B, Husstedt IW. Dynamic changes of cognitive habituation and serotonin metabolism during the migraine interval. Cephalalgia 1999; 19: 485-491.

Fischer C, Morlet D, Bouchet P, Luaute J, Jourdan C, Salord F. Mismatch negativity and late auditory evoked potentials in comatose patients. Clin Neurophysiol 1999; 110: 1601-1610.

Folstein JR, Van Petten C. Influence of cognitive control and mismatch on the N2 component of the ERP: a review. Psychophysiology 2008; 45: 152-170.

Guthrie D, Buchwald JS. Significance testing of difference potentials. Psychophysiology 1991; 28: 240-244.

Halgren E, Sherfey J, Irimia A, Dale AM, Marinkovic K. Sequential temporo-fronto-temporal activation during monitoring of the auditory environment for temporal patterns. Hum Brain Mapp 2011; 32: 1260-1276.

ICHD. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004; 24 Suppl 1: 9-160.

Judit A, Sandor PS, Schoenen J. Habituation of visual and intensity dependence of auditory evoked cortical potentials tends to normalize just before and during the migraine attack. Cephalalgia 2000; 20: 714-719.

Jung J, Morlet D, Mercier B, Confavreux C, Fischer C. Mismatch negativity (MMN) in multiple sclerosis: An event-related potentials study in 46 patients. Clin Neurophysiol 2006; 117: 85.

Kiehl KA, Laurens KR, Duty TL, Forster BB, Liddle PF. Neural sources involved in auditory target detection and novelty processing: an event-related fMRI study. Psychophysiology 2001; 38: 133-142.

Korostenskaja M, Pardos M, Kujala T, Rose DF, Brown D, Horn P, et al. Impaired auditory information processing during acute migraine: a magnetoencephalography study. Int J Neurosci 2011; 121: 355-365.

Kropp P, Gerber W-D. Prediction of migraine attacks using a slow cortical potential, the contingent negative variation. Neuroscience Letters 1998; 257: 73-76.

Kropp P, Gerber WD. Is increased amplitude of contingent negative variation in migraine due to cortical hyperactivity or to reduced habituation? Cephalalgia 1993; 13: 37-41.

Kropp P, Gerber WD. Contingent negative variation during migraine attack and interval: evidence for normalization of slow cortical potentials during the attack. Cephalalgia 1995; 15: 123-128; discussion 178-129.

Lyytinen H, Blomberg AP, Näätänen R. Event-related potentials and autonomic responses to a change in unattended auditory stimuli. Psychophysiology 1992; 29: 523-533.

Maertens de Noordhout A, Timsit-Berthier M, Timsit M, Schoenen J. Contingent negative variation in headache. Ann Neurol 1986; 19: 78-80.

Main A, Dowson A, Gross M. Photophobia and phonophobia in migraineurs between attacks. Headache 1997; 37: 492-495.

Main A, Vlachonikolis I, Dowson A. The wavelength of light causing photophobia in migraine and tension-type headache between attacks. Headache 2000; 40: 194-199.

Mazzotta G, Alberti A, Santucci A, Gallai V. The event-related potential P300 during headache-free period and spontaneous attack in adult headache sufferers. Headache 1995; 35: 210-215.

Mickleborough MJ, Hayward J, Chapman C, Chung J, Handy TC. Reflexive attentional orienting in migraineurs: The behavioral implications of hyperexcitable visual cortex. Cephalalgia 2011a; 31: 1642-1651.

Mickleborough MJ, Truong G, Handy TC. Top-down control of visual cortex in migraine populations. Neuropsychologia 2011b; 49: 1006-1015.

Mulder EJCM, Linssen WHJP, Passchier J, De Geus EJC. Interictal and Postictal Contingent Negative Variation in Migraine Without Aura. Headache 2001; 41: 72-78.

Näätänen R. Mismatch negativity: clinical research and possible applications. Int J Psychophysiol 2003; 48: 179-188.

Näätänen R, Gaillard AWK. The orienting reflex and the N2 deflection of the event-related potential (ERP). In: Gaillard AWK and Ritter W, editors. Tutorials in ERP Research : endogenous components North Holland Publishing Company, 1983**:** 119-141.

Naatanen R, Kujala T, Escera C, Baldeweg T, Kreegipuu K, Carlson S, et al. The mismatch negativity (MMN)--a unique window to disturbed central auditory processing in ageing and different clinical conditions. Clin Neurophysiol 2012; 123: 424-458.

Näätänen R, Kujala T, Winkler I. Auditory processing that leads to conscious perception: a unique window to central auditory processing opened by the mismatch negativity and related responses. Psychophysiology 2011; 48: 4-22.

Näätänen R, Paavilainen P, Rinne T, Alho K. The mismatch negativity (MMN) in basic research of central auditory processing: a review. Clin Neurophysiol 2007; 118: 2544-2590.

Näätänen R, Paavilainen P, Tiitinen H, Jiang D, Alho K. Attention and mismatch negativity. Psychophysiology 1993; 30: 436-450.

Näätänen R, Picton T. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 1987; 24: 375-425.

Näätänen R, Simpson M, Loveless NE. Stimulus deviance and evoked potentials. Biol Psychol 1982; 14: 53-98.

Näätänen R, Tervaniemi M, Sussman E, Paavilainen P, Winkler I. "Primitive intelligence" in the auditory cortex. Trends Neurosci 2001; 24: 283-288.

Näätänen R, Winkler I. The concept of auditory stimulus representation in cognitive neuroscience. Psychol Bull 1999; 125: 826-859.

Oelkers R, Grosser K, Lang E, Geisslinger G, Kobal G, Brune K, et al. Visual evoked potentials in migraine patients: alterations depend on pattern spatial frequency. Brain 1999; 122: 1147-1155.

Omland PM, Nilsen KB, Uglem M, Gravdahl G, Linde M, Hagen K, et al. Visual Evoked Potentials in Interictal Migraine: No Confirmation of Abnormal Habituation. Headache 2013.

Polich J, Criado JR. Neuropsychology and neuropharmacology of P3a and P3b. Int J Psychophysiol 2006; 60: 172-185.

Ritter W, Paavilainen P, Lavikainen J, Reinikainen K, Alho K, Sams M, et al. Event-related potentials to repetition and change of auditory stimuli. Electroencephalogr Clin Neurophysiol 1992; 83: 306-321.

Ruby P, Caclin A, Boulet S, Delpuech C, Morlet D. Odd sound processing in the sleeping brain. J Cogn Neurosci 2008; 20: 296-311.

Sams M, Alho K, Näätänen R. Short-term habituation and dishabituation of the mismatch negativity of the ERP. Psychophysiology 1984; 21: 434-441.

Sand T, Vanagaite Vingen J. Visual, long-latency auditory and brainstem auditory evoked potentials in migraine: relation to pattern size, stimulus intensity, sound and light discomfort thresholds and pre-attack state. Cephalalgia 2000; 20: 804-820.

Schoenen J, Ambrosini A, Sandor PS, Maertens de Noordhout A. Evoked potentials and transcranial magnetic stimulation in migraine: published data and viewpoint on their pathophysiologic significance. Clin Neurophysiol 2003; 114: 955-972.

Schoenen J, Wang W, Albert A, Delwaide PJ. Potentiation instead of habituation characterizes visual evoked potentials in migraine patients between attacks. European Journal of Neurology 1995; 2: 115-122.

Schwartze M, Rothermich K, Schmidt-Kassow M, Kotz SA. Temporal regularity effects on pre-attentive and attentive processing of deviance. Biol Psychol 2011; 87: 146-151.

Siniatchkin M, Gerber WD, Kropp P, Vein A. How the brain anticipates an attack: a study of neurophysiological periodicity in migraine. Funct Neurol 1999; 14: 69-77.

Siniatchkin M, Gerber WD, Kropp P, Voznesenskaya T, Vein AM. Are the periodic changes of neurophysiological parameters during the pain-free interval in migraine related to abnormal orienting activity? Cephalalgia 2000; 20: 20-29.

Snyder E, Hillyard SA. Long-latency evoked potentials to irrelevant, deviant stimuli. Behav Biol 1976; 16: 319-331.

Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia 2007; 27: 193-210.

Tervaniemi M, Lehtokoski A, Sinkkonen J, Virtanen J, Ilmoniemi RJ, Näätänen R. Test-retest reliability of mismatch negativity for duration, frequency and intensiy changes. Clin Neurophysiol 1999; 110: 1388-1393.

Valeriani M, Galli F, Tarantino S, Graceffa D, Pignata E, Miliucci R, et al. Correlation between abnormal brain excitability and emotional symptomatology in paediatric migraine. Cephalalgia 2009; 29: 204-213.

Vingen JV, Sand T, Stovner LJ. Sensitivity to various stimuli in primary headaches: a questionnaire study. Headache 1999; 39: 552-558.

Wang W, Schoenen J. Interictal potentiation of passive "oddball" auditory event-related potentials in migraine. Cephalalgia 1998; 18: 261-265; discussion 241.

Wang W, Schoenen J, Timsit-Berthier M. Cognitive functions in migraine without aura between attacks: a psychophysiological approach using the "oddball" paradigm. Neurophysiol Clin 1995; 25: 3-11.

Wang W, Timsit-Berthier M, Schoenen J. Intensity dependence of auditory evoked potentials is pronounced in migraine: an indication of cortical potentiation and low serotonergic neurotransmission? Neurology 1996; 46: 1404-1409.

Wang W, Wang GP, Ding XL, Wang YH. Personality and response to repeated visual stimulation in migraine and tension-type headaches. Cephalalgia 1999; 19: 718-724; discussion 697-718.

Woods DL, Elmasian E. The habituation of event-related potentials to speech sounds and tones. Electroencephalogr Clin Neurophysiol 1986; 65: 446-459.

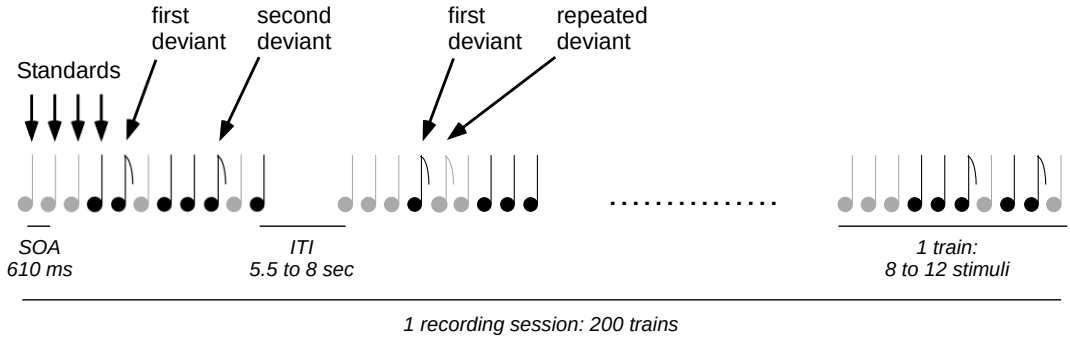

Figure 1: Design and timing of the auditory stimulation paradigm.
In each recording session, 200 trains of 8 to 12 tone bursts are presented with an inter-train interval (ITI) ranging between 5.5 and 8 seconds. Within-train stimulus onset asynchrony (SOA) is 610 ms. Two deviants (tone-bursts shorter than the standard stimuli) are presented in each train. In 50% of the trains, at least 2 standards are presented between the first and the second deviant (as for example in the first train of the figure). In the other 50% of the trains, the second deviant immediately follows the first one (repeated deviant, as in the second train of the figure). "Generic deviants" (colored in black) exclude the repeated deviants (colored in grey). "Generic standards" (colored in black) exclude the first 3 stimuli of the trains and the standard stimuli following a deviant (colored in grey).

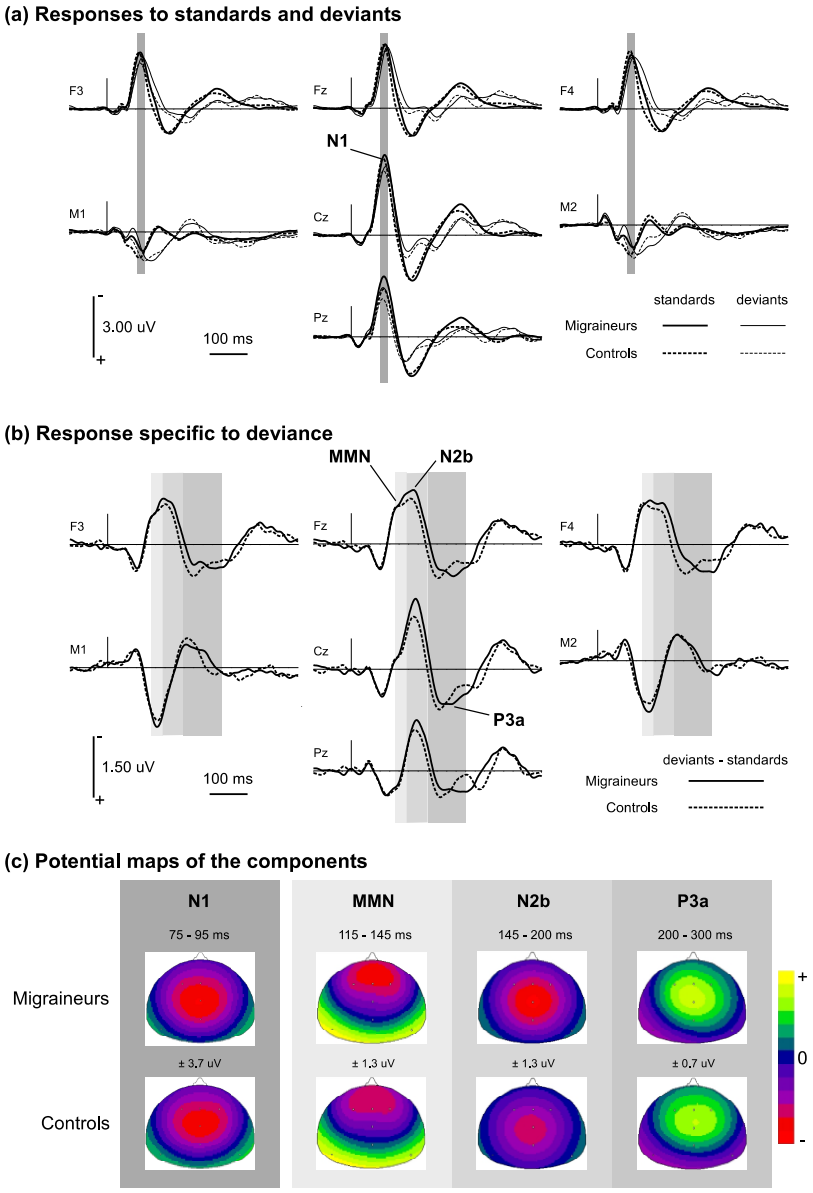

Figure 2:
(a): Responses to generic standard stimuli (thick lines) and to generic deviant stimuli (thin lines) grand averaged over the 3 sessions for 20 healthy subjects (dotted lines) and for 22 migraine patients (plain lines). The shaded area displays the temporal window defined for the assessment of sensory N1 (75-95 ms).
(b): Deviance-specific response (generic deviant minus generic standard) grand averaged over the 3 sessions for 20 healthy subjects (dotted line) and for 22 migraine patients (plain line). The shaded areas display the temporal windows defined for the assessment of MMN (115-145 ms), N2b (145-200 ms) and P3a (200-300 ms).
(c): Scalp potential maps indicative of the topographies of the different components (sensory N1 to standards, MMN, N2b and P3a in the deviance-specific response). These maps were drawn using spherical spline interpolation from the potentials measured at the seven scalp electrodes, averaged in the different time-windows in migraine patients and in healthy subjects. The range of voltage values used for the color scale is mentioned for each time-window.

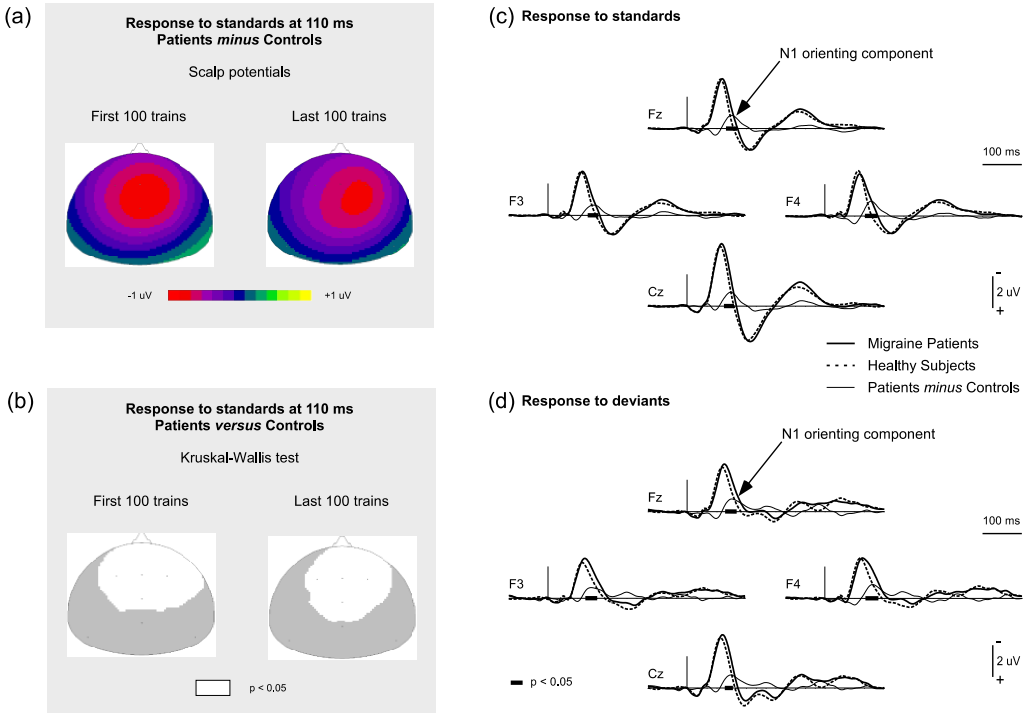

Figure 3: Investigation of the N1 orienting component.
(a) Map of the difference between healthy subjects and migraine patients in the response to standards grand averaged over the first and the last 100 trains of the 3 sessions at 110 ms, i.e. around the latency of the difference maximum.
(b) Map of the p values of the Kruskal-Wallis test comparing the response to standards in healthy subjects and in migraine patients at 110 ms in the grand average of the first half and the last half of the trains of the 3 sessions.
(c) Response to standard stimuli grand averaged over the 3 sessions for 20 healthy subjects (thick dotted lines) and for 22 migraine patients (thick plain lines) at the 4 frontal-central electrodes (F3, Fz, F4 and Cz).
(d) Response to deviant stimuli grand averaged over the 3 sessions for 20 healthy subjects (thick dotted lines) and for 22 migraine patients (thick plain lines) at the 4 frontal-central electrodes (F3, Fz, F4 and Cz).
In (c) and (d), at each electrode, the difference curve between the two populations (Patients minus Controls) is plotted with a thin line and the thick line over the x-axis denotes the temporal window in which point-by-point Kruskal-Wallis tests shows a significant difference between patients and controls.

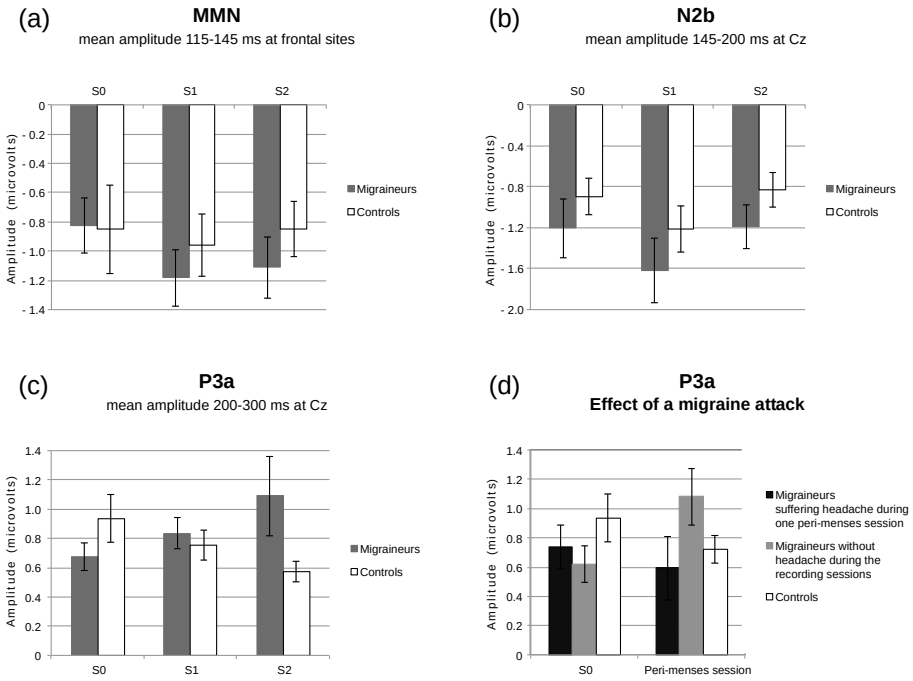

Figure 4: Mean amplitude for each session of the different components measured in the deviance-specific response (response to the generic deviant minus response to the generic standard). The black lines denote the standard error of the mean.
In (a), (b), (c), the measures are displayed for each session in migraine patients and in controls, for: (a) MMN (mean value in the 115 - 145 ms time-window at the 3 frontal electrodes), (b) N2b (mean value in the 145 - 200 ms time-window at Cz) and (c) P3a (mean of positive values in the 200 - 300 ms time-window at Cz). S0 = session 0, S1 = session 1, S2 = session 2.
In (d), P3a was measured in 3 groups of subjects: 10 patients who showed no migraine attack during the recording sessions, 11 patients who suffered headache during one peri-menses session, and the 20 control subjects. The measures are displayed for the session between menses (S0) and for a peri-menses session (the session with headache for the patients experiencing an attack during recording and a randomly chosen peri-menses session (S1 or S2) for the other two groups).

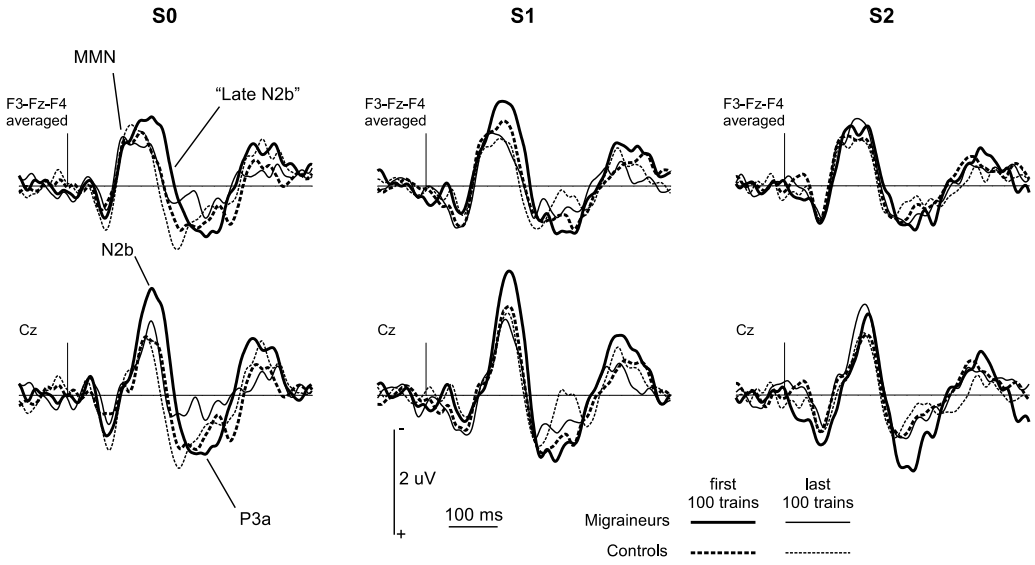

Figure 5: Long-term habituation of the response to deviance: difference response (generic deviant minus generic standard) averaged for 22 patients (plain lines) and for 20 healthy subjects (dotted lines), in the first (thick lines) and in the last (thin lines) 100 trains in each of the 3 recording sessions (S0: Session 0, S1: Session 1, S2: Session 2). Top row: response averaged over the 3 frontal electrodes, bottom row: response at Cz.

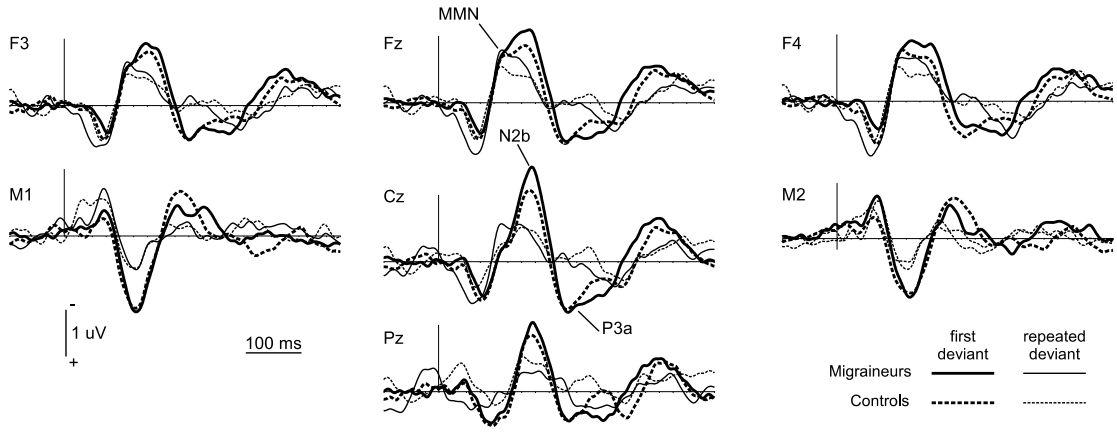

Figure 6: "Short-term habituation" of the response to deviance: difference ERPs (deviant minus standard) restricted to the first deviants in the blocks (thick lines) and to the deviants immediately following the first deviant (repeated deviants, thin lines) averaged over the 3 recording sessions, for 22 patients (plain lines) and for 20 healthy subjects (dotted lines).

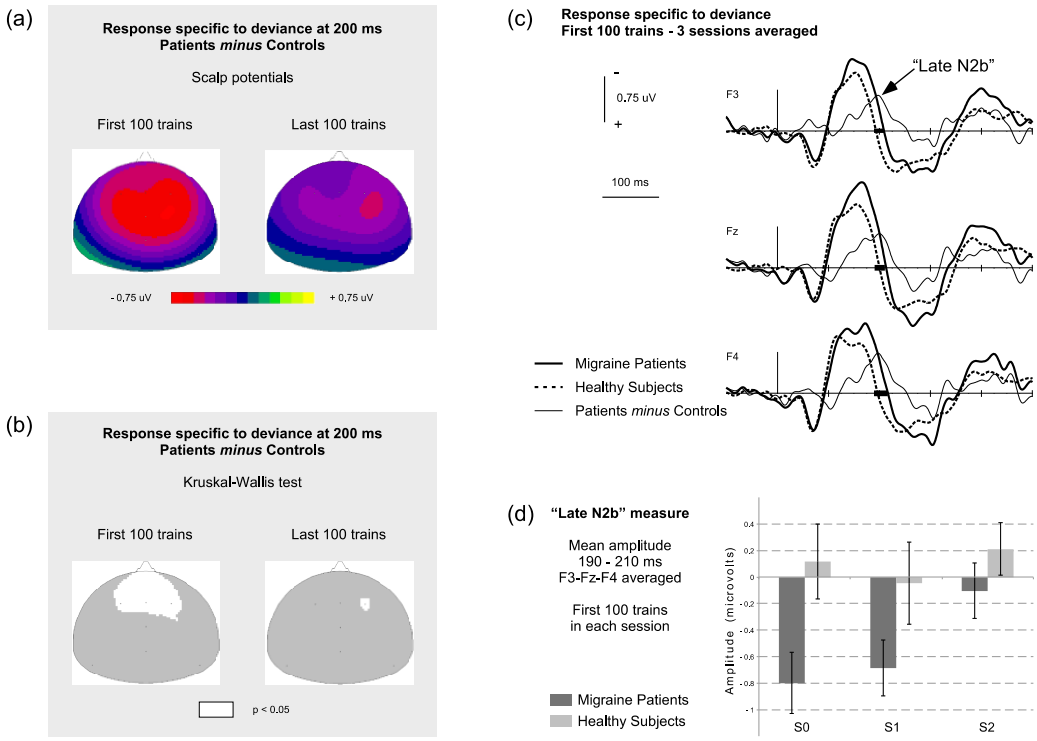

Figure 7: Investigation of the "late N2b".
(a) Map of the difference between healthy subjects and migraine patients in the deviance-specific responses (generic deviants minus generic standards) in the first and the last 100 trains, averaged over the 3 sessions at 200 ms, i.e. at the latency of the difference maximum.
(b) Map of the p values of the Kruskal-Wallis test comparing the deviance-specific responses in healthy subjects and in migraine patients at 200 ms in the first half and the second half of the trains averaged over the 3 sessions.
(c) Deviance-specific response grand averaged over the first 100 trains of the 3 sessions for 20 healthy subjects (thick dotted lines) and for 22 migraine patients (thick plain lines) at the 3 frontal electrodes (F3, Fz and F4). At each electrode, the difference curve between the two populations (Patients minus Controls) is plotted with a thin line and the thick line over the x-axis denotes the temporal window in which the point-by-point Kruskal-Wallis tests show a significant difference between patients and controls.
(d) "Late N2b" amplitude (mean value and standard error of the mean in the 190 - 210 ms time-window averaged over the 3 frontal electrodes) for each population and for the 100 first trains of each session. S0 = session 0, S1 = session 1, S2 = session 2.

Table 1

	Sensory N1 Cz (75 - 95 ms)			N1 Orienting Component F3 + Fz + F4 + Cz (100 - 120 ms)		
	F	ε - GG	p	F	ε - GG	p
Pathology (1,40)	*0 .2609*		*0 .612*	*11.317*		***0.002***
Session (2,80)	0 .123	0 .889	0 .862	0.503	*0.996*	0.606
Session x Pathology (2,80)	*0 .337*	*0 .889*	*0 .690*	*0.366*	*0.996*	*0.693*
LTH (1,40)	85 .385	1 .000	**<0 .001**	27.125	1.000	**<0.001**
LTH x Pathology (1,40)	*0 .939*	*1 .000*	*0 .338*	*0.031*	*1.000*	*0.861*
Type (1,40)	40 .633	1 .000	**<0 .001**	21.350	1.000	**<0.001**
Type x Pathology (1,40)	*0 .085*	*1 .000*	*0 .772*	*0.020*	*1.000*	*0.888*
Session x LTH (2,80)	1 .013	0 .948	0 .364	0.335	0.958	0.707
Session x LTH x Pathology (2,80)	*1 .261*	*0 .948*	*0 .288*	*0.106*	*0.958*	*0.891*
Session x Type (2,80)	0 .237	0 .992	0 .788	0.195	0.966	0.816
Session x Type x Pathology (2,80)	*0 .245*	*0 .992*	*0 .781*	*0.163*	*0.966*	*0.843*
LTH x Type (1,40)	0 .202	1 .000	0 .656	0.029	1.000	0.865
LTH x Type x Pathology (1,40)	*1 .683*	*1 .000*	*0 .202*	*1.264*	*1.000*	*0.268*
Session x LTH x Type (2,80)	0 .401	0 .996	0 .670	0.553	0.979	0.574
Session x LTH x Type x Pathology (2,80)	*2 .382*	*0 .996*	*0 .099*	*0.119*	*0.979*	*0.884*

Table 1: Results of the four-way ANOVAs on the amplitudes of the N1 sub-components, with Pathology as between-subject factor and with Session (S0, S1, and S2), Long-Term Habituation (LTH: first half versus second half of the recording session) and Type of stimulus (standard versus deviant) as within-subject factors. Degrees of freedom for each factor are indicated in parenthesis. Sensory N1 was measured at Cz in the 75-95 ms time-window where the maximal amplitude is observed in the grand average response (see Figure 2) and orienting component was measured at the 4 frontal-central electrodes in the 100-120 ms latency range, i.e., in the spatio-temporal window where a significant between-group difference was observed with Kruskal-Wallis tests (see Figure 3). Results involving Pathology are printed in italics. Significant p values ($p \leq 0.05$) are printed in bold.

Table 2

	MMN F3 + Fz + F4 (115-145 ms)			N2b Cz (145-200 ms)			P3a Cz (200-300 ms)		
	F	ε - GG	p	F	ε - GG	p	F	ε - GG	p
Pathology (1,40)	*0.139*		*0.712*	*2.219*		*0.144*	*0.078*		*0.781*
Session (2,80)	0.061	0.993	0.940	3.605	0.927	**0.035**	0.355	0.921	0.685
Session x Pathology (2,80)	*0.874*	*0.993*	*0.421*	*0.438*	*0.927*	*0.632*	*5.980*	*0.921*	***0.005***
LTH (1,40)	0.763	1.000	0.388	10.919	1.000	**0.002**	13.401	1.000	**0.001**
LTH x Pathology (1,40)	*0.164*	*1.000*	*0.688*	*2.192*	*1.000*	*0.147*	*1.920*	*1.000*	*0.174*
Session x LTH (2,80)	0.679	0.982	0.507	3.988	0.994	**0.023**	1.008	0.991	0.369
Session x LTH x Pathology (2, 80)	*0.626*	*0.982*	*0.534*	*1.753*	*0.994*	*0.180*	*0.579*	*0.991*	*0.561*

Table 2: Results of the three-way ANOVAs on the amplitudes of the different components (MMN, N2b, and P3a) of the difference response (deviant minus standard), with Pathology as between-subject factor and with Session (S0, S1, and S2) and Long-Term Habituation (LTH: first half versus second half of the session) as within-subject factors. Degrees of freedom for each factor are indicated in parenthesis. MMN was assessed as the mean amplitude at the 3 frontal electrodes between 115 and 145 ms, N2b as the mean amplitude at Cz between 145 and 200 ms and P3a as the mean amplitude of positive potentials at Cz between 200 and 300 ms. Results involving Pathology are printed in italics. Significant p values ($p \leq 0.05$) are printed in bold.

Table 3

	MMN F3 + Fz + F4 (115-145 ms)			N2b Cz (145-200 ms)			P3a Cz (200-300 ms)		
	F	ε - GG	p	F	ε - GG	p	F	ε - GG	p
Pathology (1,40)	*0.366*		*0.548*	*0.855*		*0.361*	*1.418*		*0.241*
Session (2,80)	0.116	*0.997*	*0.890*	2.410	0.952	0.099	1.058	0.974	0.350
Session x Pathology (2,80)	*0.282*	*0.997*	*0.755*	*0.205*	*0.952*	*0.805*	*1.572*	*0.974*	*0.215*
STH (1,40)	12.375	1.000	**0.001**	37.886	1.000	**< 0.001**	49.620	1.000	**< 0.001**
STH x Pathology (1,40)	*0.675*	*1.000*	*0.416*	*4.144*	*1.000*	***0.048***	*0.000*	*1.000*	*0.995*
Session x STH (2,80)	0.130	0.834	0.842	0.620	0.994	0.540	0.664	0.873	0.499
Session x STH x Pathology (2, 80)	*0.614*	*0.834*	*0.516*	*0.206*	*0.994*	*0.813*	*7.763*	*0.873*	***0.001***

Table 3: "Short-term habituation" of the main components of the difference response (this analysis does not relate to short-term habituation in a classical sense, but rather examines how repeating a deviant alters the deviant-specific response, see Introduction): results of the three-way ANOVAs on the amplitudes of MMN, N2b and P3a, with Pathology as between-subject factor and with Session (S0, S1, and S2) and Short-Term Habituation (STH, first deviant versus repeated deviant) as within-subject factors. Degrees of freedom for each factor are indicated in parenthesis. MMN was assessed as the mean amplitude at the 3 frontal electrodes between 115 and 145 ms, N2b as the mean amplitude at Cz between 145 and 200 ms and P3a as the mean amplitude of positive potentials at Cz between 200 and 300 ms as in Table 2. Results involving Pathology are printed in italics. Significant p values ($p \leq 0.05$) are printed in bold.